Xenotransplants
Using Animal Organs to Save Human Lives

Welcome

About Snapshots

We designed Snapshots to provide exactly what its title implies—a snapshot of a single area of biomedical research that lets students see how science, people, ethics, and history all fit together. Each issue has four main departments:

- Research in the News: an overview
- Story of Discovery: a brief history of the featured research
- People Doing Science: a career profile of a scientist or two
- Social Impact: a bioethics exercise

Each issue also includes a classroom activity to help students understand the scientific concepts, a short summary of the whole issue, Web links, and some good diagrams (suitable for turning into overheads) and other teaching aids.

Xenotransplants: Great Potential, Some Peril

This issue of Snapshots, our very first one, explores the promise and perils of Xenotransplantation. The potential is without doubt great. If scientists can overcome the problems of rejection, animal organs could eliminate the shortage of organs needed for transplants. People would no longer have to die waiting for a suitable human organ. Although researchers are making rapid progress toward this goal, the fact is that immune system destruction of tissue from another species is an extremely hard problem to solve. Activities one and two below help students understand the scientific problems.

The ethics of Xenotransplantation are as compex as the science. One issue is whether human beings can ethically use animal organs. This is part of the larger discussion of the proper role of animals in research.

But there is another, more subtle, ethical concern. Bacteria or viruses might cross the species barrier through the transplanted tissue, and spread from the patient to other people having nothing to do with the research. As is often the in case medical research, the risk to the patient undergoing an experimental xenotransplant is great. That risk, however, is weighed against the severity of the patient's illness. Given these high risks, only the most gravely ill patients currently participate in xenotransplant research. But risks to people not involved in the research at all have to be weighed differently. The social impact section, and Activity three below, help students work through these ethical considerations.

Using Snapshots in Class

As long as you can download, print, and photocopy the PDF version of Snapshots for your students, you can use it in class—you don't need a classroom full of computers. Some features, such as the Web links and the animated explanations, obviously demand a computer, but you don't need one in the classroom.

The teacher's instructions for each activity are given below. The student handouts are at the back of this Teacher's Guide.

Activity 1: Molecular Recognition and the Immune System

This activity gives students hands-on experience in three-dimensional model building. It's designed to help students understand the importance of molecular shape and charge in molecular-recognition, and to understand the importance of molecular recognition to immune-system function. It also provides an excellent opportunity to review the structure of cell membranes.

Objectives

- Understand the interaction between antigens and antibodies.
- Understand how molecular shape and charge allow specific molecular interactions.
- Design and build 3-D visual models to represent molecular-recognition events.
- Diagram the structure of cell membranes.
- Understand how scientists use molecular models to design therapeutic drugs.

Materials

Each student or student group should have:

- Two 40-to-50 cm lengths of easily bendable wire that will hold a shape. 20-gauge wire used for floral arrangements works well and is available in many craft stores. (Warning: the ends of the wire can be dangerous. Have students wear goggles, and fold the ends of each wire back slightly to round them off).
- A copy of the student version of the activity, including the Sample Cell Membrane Diagram
- Scissors and paper
- Scotch tape
- Pencil

Suggestions

- Have students read the "Research in the News" article from the Xenotransplantation issue of Snapshots as homework.
- Before beginning the activity, briefly review with the students the unique structure of proteins, cell membranes, and antigen-antibody interactions in the immune response, as well as the diagrams in the student activity.
- Have students work in small groups or pairs.
- The students' antigens should traverse both phospholipid-layers of the membrane and expose a unique shape on the outer membrane face.

Activity 2: The Rejection Cascade

This activity will introduce students to the events that occur during hyperacute and acute rejection of a xenograft, such as when an organ from a baboon or pig is transplanted into a human. Many of the complex aspects of the subject have been deliberately removed. For instance, there is no direct reference to MHC I and II antigens, the specific role of T and B cells, or the nature of the complement proteins. You may want to insert these topics to tailor the activity to the level of your students. But even with simplification, the topic will likely require some classroom discussion.
You might also want to review the meaning of "species-specific antigens" and add a brief discussion of the role of the genetic similarity of donor and recipient. The closer two organisms are genetically, the more likely a transplant will be successful.

Objectives

- Understand the nature of species-specific antigens.
- Recognize the difference between hyperacute rejection through the complement system and acute rejection through cell-mediated immunity.
- Place the events involved in hyperacute rejection of a xenotransplanted organ in the proper order.
- Understand the impact of different xenograft antirejection strategies

Materials

Copies of the handout for each student
Scissors

Preparation

Make a copy of the handout for each student. You might want to cut the "titles" and "diagrams" out for your students ahead of time with a paper cutter. Also, you could make a reusable classroom set of the diagrams in color by printing out multiple copies on a color printer, cutting out the diagrams, and laminating them in plastic.

Procedure

Have students read the "Research in the News" article on Xenotransplantation in Snapshots as homework. After going over some of the key ideas in class, have students separate into groups of two to four. After cutting out the captions and diagrams, students should collaboratively pair the captions with the diagrams and put them in an order that makes sense for a presentation about xenotransplant rejection. (It may be possible to come up with an order other than the one listed below, although major deviation would result in a poorly organized talk.) Choose one group to present their ordering scheme. This activity would also make a good extra-credit project for a motivated student. Ask the student to do the activity as homework, then present to the class.

Answer

If you numbering the pictures on the student handout left to right, top to bottom, a correct order for the pictures is:
11, 9, 1, 8, 10, 7, 4, 6, 5, 2, 3, 12

A correct order for the captions is:
2, 5, 4, 8, 7, 6, 1, 12, 3, 10, 9, 11

The picture series 11, 9, 1, 8, 10, 7, 4 explains hyperacute rejection, mediated by complement and membrane attack complexes. Series 6, 5, 2, 3, 12 explains the cell-mediated immune attack mechanism.

You Look Familiar

Molecular Recognition in Immunity

By Fred Sculco, Morrison Chair in Science, Noble and Greenough School,
and Wright Fellow in Innovative Science Education 1999–2000, Tufts University*

Introduction

Molecular recognition—the process by which one molecule binds to its specific target and to no other molecule—is a key concept in biology. Our own survival depends on millions of carefully choreographed molecular-recognition events occurring each and every second of our lives. For example, the abilities of an enzyme to attach to its substrate, and a hormone to attach to its cellular receptor, and even a virus to attach to a host cell, all depend upon molecular recognition. **(See Figure 1)**.

The immune system defends the body against foreign invaders. It, too, relies on molecular recognition. Specifically, the immune system must distinguish proteins and other molecules on the surfaces of our cells from molecules on the surfaces of cells that don't belong. Special proteins in the blood called antibodies are one way the immune system spots foreign invaders such as bacteria, fungi, protozoa, and viruses. Your body can make thousands of different antibodies. Each different antibody recognizes and binds to one specific foreign molecule, called an antigen.

Immune recognition also causes rejection of organ transplants. The recipient's immune system recognizes proteins on the surfaces of the cell membranes of the transplanted organ as foreign. It then mounts an all-out war to rid the body of these foreign antigens, and in the process destroys the transplant. Controlling this destructive recognition process is the key to successful organ transplantation.

Scientists often rely on models in order to visualize how complex molecular structures such as antigens and antibodies recognize each other. (You might remember that Watson and Crick built models to figure out the double-helix structure of DNA.) In this activity you'll make a model of an antibody and its target antigen. In the process you'll demonstrate that antibodies possess not only unique **shapes** that aid in attaching them to antigens but also unique patterns of **charges,** positive and negative areas resulting from electrons and protons in the molecule. For an antibody to successfully bind its target antigen, both shape and charge must fit together.

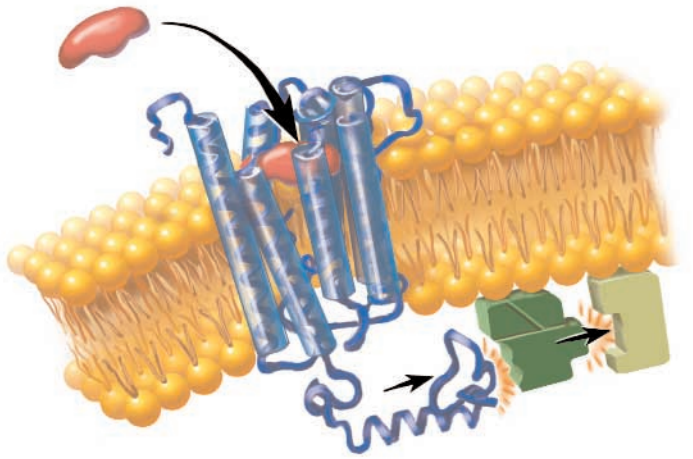


Figure 1. A schematic diagram showing a hormone binding to it's cell surface receptor. The hormone binds to the outside surface of the receptor protein, causing the receptor inside the cell to change shape slightly. This allows the receptor to bind another intermediate protein inside the cell, which is turn recognizes and binds yet another protein. The last protein then catalyzes a reaction that changes the stae of the cell. Each element in this chain must fit its partner precisely for this chain of events to work..

A. Molecular Shapes of Antigens and Antibodies

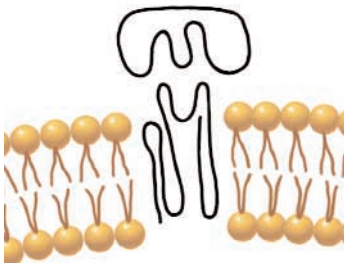


Figure 2: A sample model shape.

1) Find the sheet of paper entitled "Sample Cell Membrane" in this packet. The drawing of the membrane on this sheet shows only the phospholipid layers, with no other molecules embedded. Note, however, the gap in the membrane where you'll supply a model protein antigen.

2) Your teacher has given you two pieces of bendable wire. Use one of these to design a protein-antigen shape that will fit in the space on the membrane. **(Warning: the ends of the wire can, literally, "put your eye out." Be careful. Wear goggles, and bend the ends of each wire back slightly to round them off.)** Your protein antigen should span both phospholipid layers of the membrane. The wire should also lie flat on the page—this is a two-dimensional model. Using clear plastic tape, attach your shape to the sheet of paper in the space provided in the membrane. Figure 2 shows an example—but you can be a bit more adventurous in making your shape.

3) Exchange the paper containing your antigen model with another team. Use your second piece of wire to create an antibody that would recognize and attach to the model antigen from the other team. Remember that antibodies have access only lto the part of the antigen that is poking outside the cell.

Question: Was the antibody molecule the other group designed to recognize your membrane antigen the same as you had envisioned? Is there only one specific shape that will attach and fit into the molecular shape of your antigen?

B. Molecular Charge—the Rest of the Story

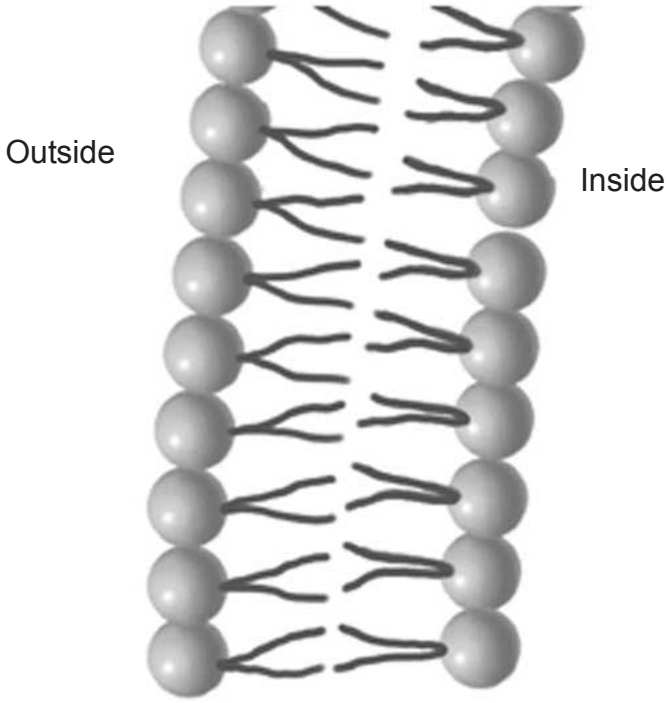
The fact that several different molecules could have a shape that would make a reasonable fit onto the antigen molecule you made in Part A may seem confusing. Clearly, this would destroy the concept of specific molecular recognition. In biological systems, however, shape alone doesn't determine whether two molecules will bind together. Small charged areas on molecules—created by slight separations between protons and electrons—also play an important part in molecular recognition. These charged areas create an array of positive (+) and negative (-) locations on the surface of the molecule. Because like charges repel each other, and opposite charges attract, the precise location of the charged areas on the antigen and the antibody make a huge difference in whether the two will stick together. It is the combination of both **shape and charge** that allows the specificity of molecular recognition events.

1) First you will add some negative and positive charges to the antigen molecules you made in your cell membrane. Look over the shape of your antigen. Using a pencil, draw five charged areas at random locations and in any arrangement you like**.** Don't let other teams see the charge array you have drawn.

2) Tape the antibody molecule you made in Part A onto a small piece of paper. Now use a pencil to draw five charged areas on your antibody.

3) Again, exchange your charged antibody model with another team. Unless somebody peeked or got incredibly lucky, the charges on the model antibodies won't correspond with the charges on the antigens. Erase the incorrectly placed charges on the other team's antibody, and draw new charges that would help the antibody and antigen bind.

Questions: Which would bind more tightly, two molecules with highly complementary shapes but no surface charges, or these same two molecules that also have an array of complementary charges? How might scientists use knowledge of molecular shape and charge to design a molecule that could be used as a drug to interfere with the binding of an antigen and an antibody?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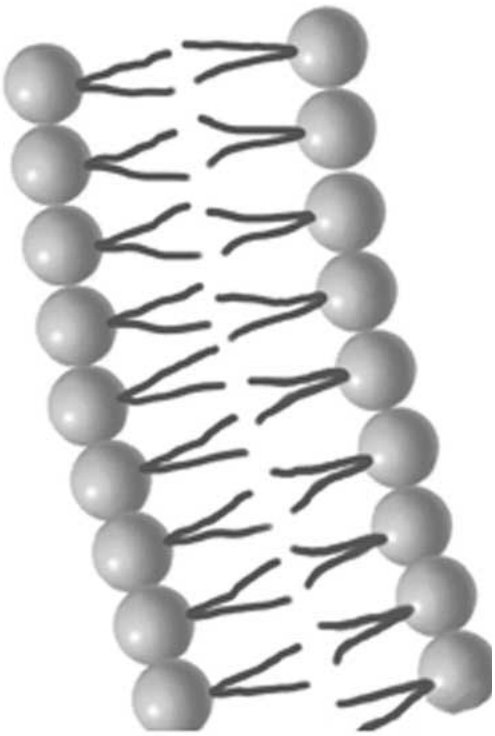
Inside



The Xenotransplant Rejection Cascade

By Fred Sculco, Morrison Chair in Science, Noble and Greenough School,
and Wright Fellow in Innovative Science Education 1999–2000, Tufts University*

Introduction
The human immune system is our own "personal bodyguard." Like any good defender, it must recognize "the enemy"-that wide range of viruses, bacteria, fungi, protozoa and other would-be pathogens that we encounter every day. At the same time, the immune system must be able to distinguish friend from foe. (A guard that instantly attacks anything that moves is probably not someone you'd want in your home.)

Our immune system is genetically programmed to recognize certain proteins on our cells (self) from the thousands of invading pathogens (nonself) trying to gain a foothold in our body. But how is the immune system able to differentiate between friend and foe?

Recognition of the Body's Own Cells
Cells posses unique antigenic proteins on their membranes that are like fingerprints; no two people (except identical twins) have the same protein structures in their membranes. Our immune cells see these proteins as normal or "self." But if our cells are transplanted into another person, they cause an immune reaction. T and B cells mount an all-out attack in an attempt to rid the body of these foreign proteins.

The Recognition Problem in Xenotransplants
In the case of xenotransplants (transplanting organs across species), the genetic separation between donor and recipient is even greater. Membrane-bound proteins are less similar, and the rejection of the organ is stronger, faster, and more complex. In particular, xenotransplants trigger a response called hyperacute rejection, which can destroy a transplanted organ within just a few hours.

Hyperacute rejection results from activation of a part of the immune system called the complement system, an array of proteins that circulates in the blood. When activated, the complement proteins bind together to form "membrane-attack complexes" that can poke large holes in cell membranes. The problem is that all mammals have a set of species-specific antigens on the surfaces of cells lining blood vessels. When antibodies circulating in human blood see these antigens from another species, they quickly bind onto them and activate the complement system. The membrane-attack complexes generated then destroy the blood vessels supplying the organ with nutrients. Once hyperacute rejection gets going, the organ usually doesn't survive for more than a few hours.

But even if hyperacute rejection is blocked, rejection continues at another level. The humoral (antibodies and B cells) and cellular (macrophages and T cells) arms of the immune system come into play. These components attack the transplanted organ cell by cell, and can cause the transplanted organ to fail after weeks or months.

Blocking Rejection
Scientists are exploring several strategies to short-circuit the rejection mechanisms described above.

Genetically engineer pigs so that they don't express the species-specific antigens that activate complement and hyperacute rejection.

Use drugs that suppress the immune system to prevent rejection. These immunosuppressive drugs, which do a pretty good job when used in human-to-human transplants, have to be used in such high doses that the transplant recipient is left open to infection.

Induce bone marrow chimerism. This involves replacing part of the recipient's bone marrow with bone marrow from the organ donor. Immune cells from this new bone marrow will not recognize the xenograft as foreign.

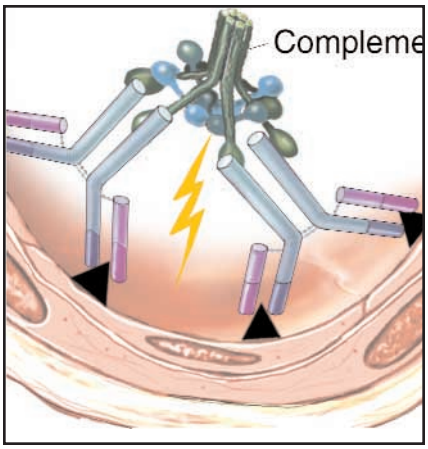
None of these strategies is perfect, but scientists continue to seek ways to improve each of them. What once seemed an impossible option, xenotransplantation, is now looked at as a real possibility in responding to the growing number of people who die while waiting for a compatible human organ transplant.

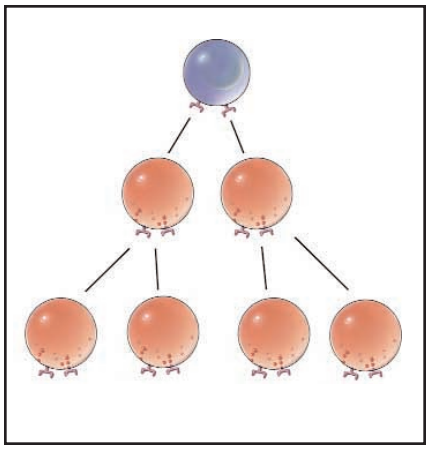
Your Challenge
Dr. Hanna Slip was on her way to your classroom to give a presentation on xenotransplant rejection and how scientists hope to avoid it. Unfortunately, a crisis intervened, and she couldn't make it (flat tire, space aliens, whatever-you decide). Fortunately, she sent her presentation slides ahead. Unfortunately, she just dropped them in a box to send them, and now they're all out of order. The attached page contains the titles of the slides, as well as a diagram for each title. Your job is to put Dr. Slip's slides back in the right order, and give the presentation in her absence.

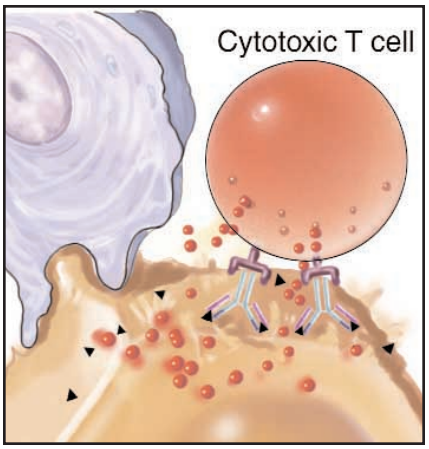
A. Using scissors, cut out the individual slide titles and slides on the attached pages. First, pair the titles with the correct slides. Then, arrange them on your desk in an order that could be used in a presentation about xenotransplant rejection.

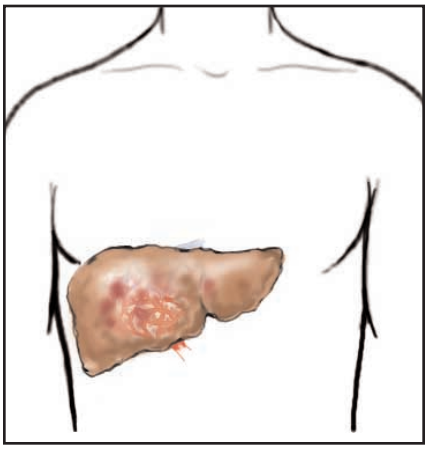
B. Using your correctly sequenced slides, discuss where in the rejection cascade genetic engineering of donor animals, immune-suppressing drugs, and induced bone marrow chimerism would reduce the risk of xenotransplant rejection.

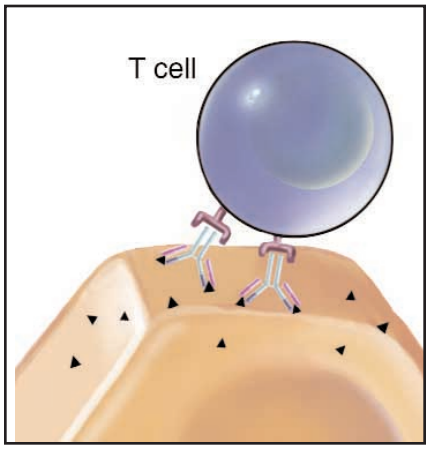
Organ dies due lack of nutrients	Pig cells display species-specific antigens on their surfaces	T cells bind to foreign antigens on xenograft cells
Complement proteins attach to the bound antibodies, and activate	Antibodies in transplant recipient's blood bind to antigens on the cells lining the transplanted organ's capillaries.	Transport of nutrients and oxygen to the xenograft cut off
Membrane attack complexes lyse (burst open) cells lining the capillaries of blood vessels in xenograft	Complement activation generates membrane attack complexes (protein complexes that poke holes in cell membranes)	Cytotoxic T cells and macrophages attack xenograft cells
Activated T cells start immune response, including expansion of number of immune cells	Organ is damaged or dies due to cell-mediated immune attack	If organ somehow survives hyperacute rejection, cell-mediated rejection mechanisms still occur

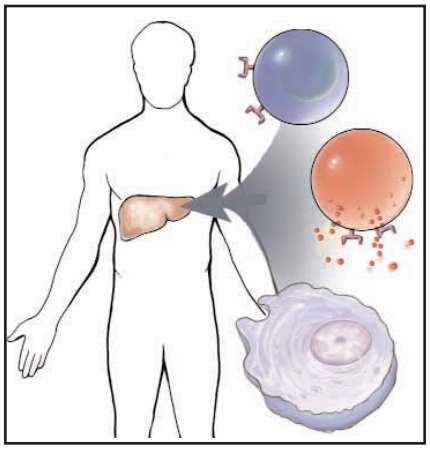

Compleme

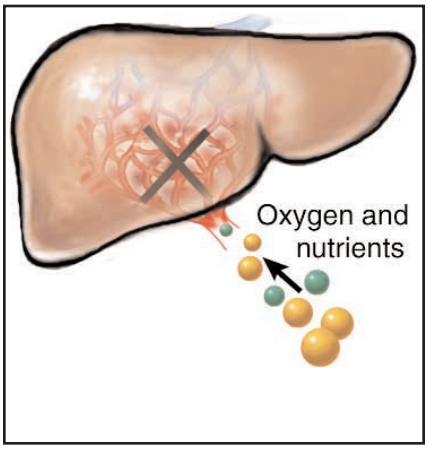


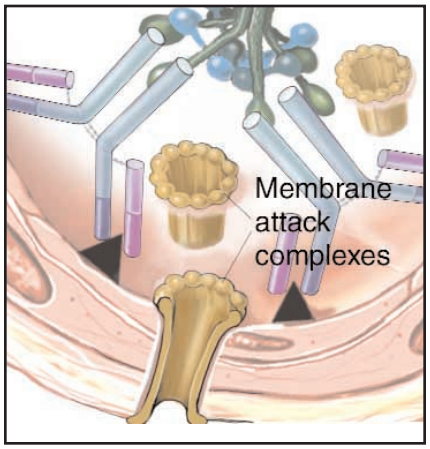

Cytotoxic T cell




T cell




Oxygen and
nutrients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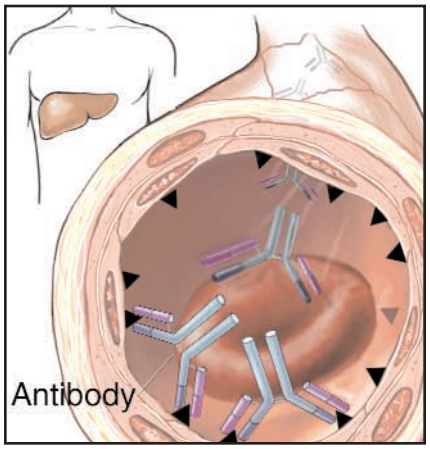
attack
complexes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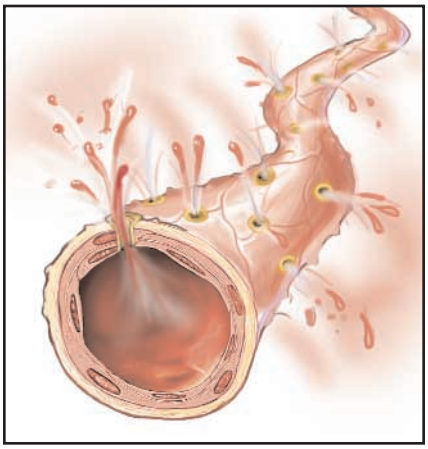

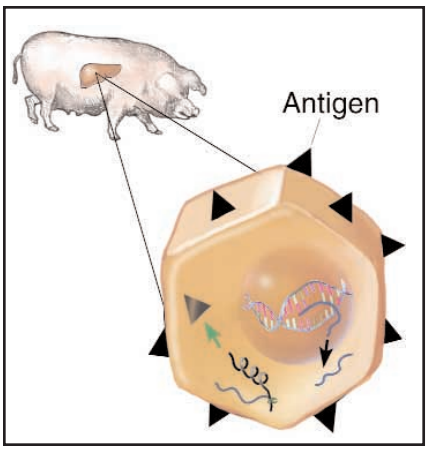
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